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Meiosis: Checking Chromosomes Pair up Properly

Faithful recombination and chromosome segregation in meiosis require regulated steps of homolog recognition and association which are monitored by meiotic checkpoints. A recent study in the nematode *Caenorhabditis elegans* has identified a checkpoint mechanism that monitors chromosome pairing during meiosis.

Bettina Meier and Anton Gartner

Finding a match is not only a fundamental problem in our lives but also a universal challenge during meiosis, the specialized cell division that generates haploid gametes from diploid parental cells. At the onset of meiosis, homologous parental chromosomes are faced with the challenge of finding each other and, ultimately, aligning along their entire length. This process goes hand in hand with meiotic recombination, which ensures the exchange of genetic information and establishment of a stable chromatin link between homologous chromosomes, termed a chiasma, which is needed for the accurate disjunction of homologous chromosomes.

As we all know, finding one's match is a knotty undertaking; things can go awfully wrong and the sequence of events has to be actively aborted, or if things look a little more favourable they may need to be interrupted to allow for adjustments to take place. During meiotic prophase, the processes prone to go wrong are the pairing of homologous chromosomes and meiotic recombination. To deal with these failures, meiotic cells have evolved checkpoint mechanisms which — dependent on the circumstances and/or the species affected — either trigger meiotic cell cycle arrest in order to allow for a problem to be rectified, or cull faulty cells by triggering their apoptotic demise. A recent study by Bhalla and Dernburg [1], on the nematode *Caenorhabditis elegans*, has defined a meiotic chromosome-pairing checkpoint that, if activated, induces germ cell apoptosis. This work is likely to be important as a large portion of human male sterility is associated with defects in homolog pairing (reviewed in [2]).

In meiotic prophase, the initial recognition and pairing of homologous chromosomes (known as synapsis-independent pairing), and the initiation of meiotic recombination (which requires Spo-11 catalyzed DNA double strand breaks) have already occurred before the stage known as pachytene. Within pachytene, the intimate association between homologs into a proteinaceous scaffold — the synaptonemal complex — is completed in a process defined as chromosome synapsis, and double strand breaks are resolved either as gene conversion or as crossover recombination events (Figure 1, top panel).

Importantly, the initial synapsis-independent pairing is needed for meiotic double strand breaks to be generated ([3] and references therein), an excessive number of which may have the potential to trigger the DNA damage checkpoint [1]. Synapsis of homologous chromosomes then allows the repair of double strand breaks (Figure 1, top panel) [4,5]. In most organisms differentiating between meiotic pairing and recombination checkpoints is a murky task, as recombination and pairing initiation go hand in hand and cannot be unequivocally mutationally separated [6–8].

This dilemma is nicely resolved by the recent study of Bhalla and Dernburg [1] who, taking advantage of the special property of *C. elegans* that meiotic chromosome pairing can occur unperturbed in the absence of meiotic recombination [9], have unequivocally identified a chromosome pairing checkpoint, demonstrated its *in vivo* importance and implicated two specific gene products in the process [1]. Their study builds on previous work which defined a meiotic DNA damage and recombination checkpoint that uses conserved proteins, such as Hus-1 and the *C. elegans* p53 orthologue Cep-1, to trigger apoptosis [10–13].

Armed with these tools, Bhalla and Dernburg [1] began by addressing whether apoptosis of pachytene cells is enhanced in various mutants where meiotic chromosome pairing and synapsis of all *C. elegans* chromosomes, or just the sex chromosomes, are affected [1]. Worms carrying two sex chromosomes, the X chromosomes, develop as hermaphrodites, whereas those with just one X chromosome develop as males.

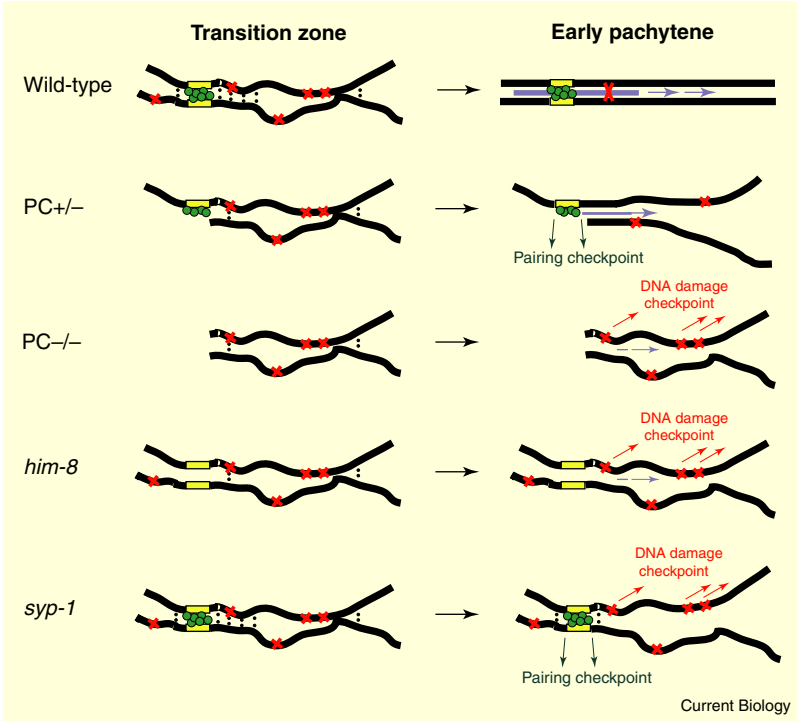

Figure 1. Meiotic pairing defects in various mutant situations.

For simplicity, only X chromosome pairing in the transition zone and in early pachytene are shown. Activation of the DNA damage checkpoint and the pairing checkpoint, which is executed in late pachytene, is indicated for each mutant. X chromosomes are indicated by black lines. Local X chromosome synapsis-independent pairing indicated by black double dots is enhanced but not restricted to the pairing center (represented as yellow boxes). Him-8 protein binding is indicated by green circles. Rad-51 foci are depicted in red. Pairing center hemizygous ($PC^{+/-}$) mutants lack one pairing center, whereas $PC^{-/-}$ mutants lack both pairing centers. The level of synapsis varies between the different mutants and is schematically indicated by the thickness of the blue line representing the synaptonemal complex and by the strength and number of blue arrows.

In the first genetic situation analysed, Bhalla and Dernburg [1] studied germ cell apoptosis in a strain where one of the two hermaphrodite X chromosomes lacks its 'pairing center'. Pairing centers are *cis*-acting loci, one of which resides on each chromosome, which are required to locally stabilize pairing and promote synapsis [14,15]. In strains hemizygous for the X-chromosome pairing center, local pairing is perturbed in early meiotic prophase [14,15], reducing the frequency of synapsis to approximately 45% [1] (Figure 1).

In the second genetic situation, apoptosis was scored in strains that either lack both X chromosome pairing centers ($PC^{-/-}$ worms) or are deficient for Him-8, a pairing-center-binding protein that specifically facilitates X chromosome pairing center–pairing center interaction [16], mutations that lead to even stronger pairing defects [15,16] (Figure 1). Hemizygous and homozygous pairing center mutants, as well as *him-8* mutants, were found to exhibit similar increases in apoptosis, though surprisingly the effects in the two cases differ in their genetic requirements [1] (Figure 1). In the pairing center hemizygotes, increased apoptosis is blocked neither by prevention of double strand break generation nor by mutation in the DNA damage checkpoint pathway, but it is dependent on the *C. elegans* homologue of Pch2p, a yeast protein previously implicated in meiotic checkpoint control [1]. The failure to pair might thus be specifically sensed and affected cells might be removed from the system by the induction of germ cell apoptosis.

Consistent with this notion, Bhalla and Dernburg [1] found that the percentage of oocytes with achiasmatic X chromosomes and the corresponding incidence of males is increased in pairing center hemizygote double mutants with *ced-3* or *ced-4* — cell death genes required for (almost) all apoptosis [17] — as well as in double mutants with *pch-2*, but not in double mutants with DNA damage checkpoint pathway mutants [1]. In contrast, the elevated levels of apoptosis in *him-8* or $PC^{-/-}$ mutants are not dependent on the pairing checkpoint — they are unaffected by the *pch-2* mutation — but they are suppressed by mutations affecting the DNA damage checkpoint [1] (Figure 1), and the percentage of oocytes with achiasmatic X chromosomes was increased in *ced-4*, $PC^{-/-}$ double mutants as compared to the $PC^{-/-}$ single mutants [15]. Hence, both a pairing checkpoint and the DNA damage checkpoint can be used as a means to cull asynaptic cells.

To explain these observations, Bhalla and Dernburg [1] propose that the pairing checkpoint requires, besides Pch-2, also a pairing center and Him-8 [1]. Pairing centers and Him-8 would therefore have a role in meiotic chromosome pairing, as well as in the pairing checkpoint, whereas Pch-2 only affects the pairing checkpoint. In both pairing center hemizygotes and $PC^{-/-}$ homozygotes or *him-8* mutants, Spo-11-induced double strand breaks — or more precisely, double strand break repair intermediates — were visualized cytologically as Rad-51 foci which accumulate as a result of synapsis defects [15,16] (Figure 1).

Assuming that meiotic double strand break intermediates indeed lead to the activation of the DNA damage checkpoint, why is the DNA damage checkpoint not activated in pairing center hemizygotes, as opposed to pairing center or *him-8* homozygotes? The failure of DNA damage checkpoint activation in these cases could be due to the repression of the DNA damage checkpoint once the pairing checkpoint is activated.

Alternatively, the lower level of asynapsis in pairing center hemizygous mutants, as opposed to *PC*$^{-/-}$ or *him-8* mutants, might only generate a relatively small number of double strand break intermediates insufficient to trigger the damage checkpoint (Figure 1). Indeed, the meiotic DNA damage and pairing checkpoint is activated simultaneously in *syp-1* mutants [1].

In *syp-1* mutants, synapsis-independent pairing occurs, but synaptonemal complex formation is globally abrogated on all chromosomes, leading to largely unaligned chromosomes in pachytene that exhibit homologue associations exclusively at pairing centers [5] (Figure 1). Activation of the pachytene checkpoint in *syp-1* animals might therefore suggest that synapsis initiation, which is likely to commence at pairing centers (Figure 1), rather than local synapsis-independent pairing at the pairing centers, might be monitored by the pachytene checkpoint. To substantiate this, it will be important to further address whether the pairing checkpoint is triggered in mutants defective in pairing centers of autosomes and whether this also requires *pch-2*. If this were found to be the case, culling of meiocytes with asynaptic chromosomes would be likely to be restricted to the female meiocytes as no evidence for apoptosis in the male germ line has been reported.

In budding yeast, *pch2* was initially shown to be required for checkpoint response, based on the failure of Pch2p to mediate cell cycle arrest in *zip1* and *dmc1* mutants, which are primarily defective in meiotic pairing and in meiotic recombination, respectively [18]. A direct involvement of Pch2p in the recombination checkpoint has, however, been contested by a recent study [19] suggesting that Pch2p does not suppress the Dmc1p-triggered cell cycle arrest, but rather affects recombinational repair. Budding yeast Pch2p localizes in distinct foci on meiotic chromosomes, but mainly accumulates within the nucleolus, which contains rDNA repeats that remain largely unsynapsed in pachytene [18]. Localization of Pch2p correlates with its checkpoint function, as sir2 mutants fail to keep Pch2p in the nucleolus and are equally defective in the pachytene checkpoint [18].

How might Pch-2 function in worms to trigger apoptosis by one Him-8 bound pairing center that lacks a homologue with which to pair? It is likely that a Him-8 containing complex is bound to pairing centers before pairing is initiated [16]. By analogy to replication licensing, this Him-8-containing, pairing-center-bound complex might be needed to licence pairing and synapsis initiation at the pairing center and subsequently enhance or stabilize pairing center–pairing center interactions. In a subsequent step, recruitment of other factors might stabilize pairing and allow synapsis initiation, a step at which the pairing checkpoint might come into play. It is feasible that a 'pairing sensor' might be locally embedded at the pairing center, as synaptonemal complex formation is initiated to detect the absence of homologous pairing. Pch-2 may act as a sensor of synapsis failure or as a downstream transducer of the pairing checkpoint signal feeding to the apoptotic machinery. It will be interesting to identify further pairing checkpoint components and to asses Pch-2 localization. Finally, it is worth asking whether the mammalian Pch-2 homologue also has a role in an equivalent pairing checkpoint [20].

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